EXHIBIT I

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RISK OF COLORECTAL AND OTHER GASTRO-INTESTINAL CANCERS AFTER EXPOSURE TO NITRATE, NITRITE AND *N*-NITROSO COMPOUNDS: A FOLLOW-UP STUDY

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***N*-nitroso compounds are potent carcinogens detected in foodstuffs. The importance of dietary nitrosamines in relation to human cancer development is, however, uncertain. We studied the relationship between intake of nitrates, nitrites and *N*-nitrosodimethylamine (NDMA) and risk of cancers of the gastro-intestinal tract in a cohort of 9,985 adult Finnish men and women. During a follow-up period of up to 24 years, 189 gastro-intestinal cancer cases were diagnosed in the cohort, initially free from cancer. Intake of nitrate, nitrite and NDMA were estimated, based on food-consumption data from a 1-year dietary history interview covering the total diet of the participants. A significant positive association was observed between intake of NDMA and subsequent occurrence of colorectal cancer with a relative risk (RR) between the highest and lowest quartiles of intake of 2.12 [95% confidence interval (CI) 1.04–4.33]. Of various sources of *N*-nitroso compounds, intake of smoked and salted fish was significantly (RR = 2.58, 95% CI 1.21 − 5.51) and intake of cured meat was non-significantly (RR = 1.84, 95% CI 0.98–3.47) associated with risk of colorectal cancer. No similar association was observed for intake of other fish or other meat. No significant associations were observed between NDMA intake and cancers of the head and neck combined or of the stomach or between nitrate or nitrite intake and risk of cancers of the gastro-intestinal tract. Our results are in line with the idea that *N*-nitroso compounds can induce colorectal cancer in humans. *Int. J. Cancer* 80:852–856, 1999.**

N-nitroso compounds are potent carcinogens that can induce tumours in various animal species at a variety of sites (Forman, 1987; Tricker and Preussmann, 1991). Humans are exposed to nitrosamine compounds both from the diet and other environmental sources as well as from endogenous synthesis within the body (Mirvish, 1995; Bartsch and Spiegelhalder, 1996). *N*-nitrosodimethylamine (NDMA) and other volatile *N*-nitroso compounds have been detected in foods with added nitrates or nitrites, such as salt-preserved fish and meat, and in food processed by smoking or direct-fire drying (Scanlan, 1983; Hotchkiss, 1989).

It is plausible to hypothesize that *N*-nitroso compounds from foods represent a risk factor for cancers of the gastro-intestinal tract. This is supported by results from both ecological comparisons and case-control studies that have shown an increased risk of cancers of the stomach and upper aerodigestive tract associated with intake of foods with potentially high contents of nitrosamines, such as salted, smoked and pickled foods (Kono and Hirohata, 1996; Eichholzer and Gutzwiller, 1998). Increased risk of colorectal cancer has been associated with high consumption of processed meats in several cohort studies (Bjelke, 1980; Willett *et al.,* 1990; Giovannucci *et al.,* 1994; Goldbohm *et al.,* 1994). A few studies on the intake of NDMA and occurrence of cancers of the stomach and upper aerodigestive tract have yielded discrepant findings (Risch *et al.,* 1985; Chyou *et al.,* 1990; Gonzáles *et al.,* 1994; La Vecchia *et al.,* 1995; Pobel *et al.,* 1995; Rogers *et al.,* 1995). We investigated whether intake of NDMA or foods rich in nitrosamines is predictive for colorectal cancer or other cancers of the gastro-intestinal tract in a Finnish cohort of men and women followed up for up to 24 years.

POPULATION AND METHODS

During the period 1966–1972, the Mobile Health Clinic of the Social Insurance Institution undertook multiphasic screening examinations in several regions of Finland (Knekt, 1988). As part of the main study, detailed data about food consumption were collected from 9,985 individuals who had never had cancer, by dietary history interview (Järvinen *et al.,* 1993). Questions were asked about various food items and mixed food dishes consumed during the previous year, guided by a pre-formed questionnaire. The method of food preparation was specified. Beer consumption was included as a part of the dietary history interview for 7,041 study participants.

A detailed description of the estimation, intake and food sources of nitrates, nitrites and NDMA was presented in a previous report (Dich *et al.,* 1996). Mean daily intake of nitrates was 77 mg and that of nitrites 5.3 mg. Nitrates were provided mainly by vegetables (91.9%), whereas nitrites were derived mainly from cured meats and sausages (94.2%). Dietary NDMA was provided by smoked and salted fish (51.9%) and cured meats and sausages (48.1%). Mean daily intake of NDMA from the diet was 0.052 µ g and that from beer, estimated in a sub-population, was 0.071 µ g (Dich *et al.,* 1996).

The short-term reproducibility of the daily consumption of nitrates, nitrites and NDMA was estimated from dietary interviews repeated 4 to 8 months apart. The intraclass correlation coefficients for reproducibility were 0.48 for nitrates, 0.73 for nitrites and 0.53 for NDMA. The corresponding figures for long-term reproducibility, during a period of 4 to 7 years, were 0.36, 0.25 and 0.26. The short-term and long-term reproducibilities for smoked and salted fish were 0.63 and 0.36, respectively, and for cured meats 0.43 and 0.15, respectively.

A pre-posted questionnaire, checked at the baseline examination, yielded information on smoking habits. Subjects were classified according to smoking status as never smokers, ex-smokers, pipe or cigar smokers only, smokers of less than 15 cigarettes per day and smokers of over 15 cigarettes per day. The intraclass correlation coefficient for overall reproducibility during an interval of 4 to 7 years was 0.72 (Heliövaara *et al.,* 1993). During a maximum 24-year follow-up period from 1967 to 1990, 189 cases of cancer of

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the gastro-intestinal tract were ascertained through the nationwide Finnish Cancer Registry (Teppo *et al.*, 1980). Of these, 48 were cancers of the head and neck combined (ICD 140–148, 150, 161), 60 of the stomach (ICD 151) and 73 of the colorectum (ICD 153, 154) (World Health Organization, 1955).

Cox's proportional hazards model was used to estimate relative risks (RRs) of the association between nitrate, nitrite and NDMA intake and risk of cancer, adjusting for possible confounding factors (Kalbfleisch and Prentice, 1980). RRs were computed for quartiles of intake, using the lowest quartile as the reference category. Statistical hypotheses of trend were tested, using the likelihood ratio test based on the models. The reproducibility of the reported intakes was estimated with the intraclass correlation coefficient.

RESULTS

The RRs of cancers of head and neck combined, stomach and colorectum in categories of potential confounding factors are presented in Table I. Individuals who subsequently developed disease were older and, with the exception of colorectal cancer, more often current smokers.

The RRs of cancer between quartiles of intake of nitrates, nitrites and NDMA are presented in Table II. Dietary nitrite intake was not significantly associated with occurrence of gastro-intestinal cancers. A non-significant inverse association was observed for nitrate intake and stomach cancer. A significant positive association was present between intake of NDMA and colorectal cancer risk, the RR between the highest and lowest quartiles of intake being 2.12 [95% confidence interval (CI) 1.04–4.33]. Further adjustment for intake of β-carotene, vitamin E and vitamin C strengthened the association, giving an RR of 2.20 (95% CI 1.07–4.52). A stronger association between intake of NDMA and colorectal cancer was found in women *vs.* men, with RRs of 4.11 (95% CI 1.46–11.55) and 1.04 (95% CI 0.37–2.93), respectively. Study of possible interactions between intake of NDMA and intake of vegetables, fruits, vitamin C and vitamin E and smoking revealed no significant associations (data not shown).

A significant association between intake of smoked and salted fish and risk of colorectal cancer was observed, the RR between the highest and lowest quartiles being 2.58 (95% CI 1.21–5.51; Table III). A similar non-significant association was observed for intake of cured meat and sausages, with an RR of 1.84 (95% CI 0.98–3.47). No similar associations were observed for other fish or

TABLE I – RELATIVE RISK (RR)[1] OF CANCER BETWEEN CATEGORIES OF DIFFERENT BASELINE VARIABLES

Variable	Population at risk	Head and neck			Stomach			Colorectum		
		Number of cases	RR	95% CI	Number of cases	RR	95% CI	Number of cases	RR	95% CI
Sex										
Men	5,274	36	1		43	1		36	1	
Women	4,711	12	0.66	0.29–1.51	25	0.62	0.33–1.15	37	0.75	0.42–1.35
p value			0.32			1.13			0.35	
Age (years)										
15–49	7,228	22	1		18	1		26	1	
50–59	1,517	15	4.76	2.44–9.27	28	10.65	5.83–19.45	21	5.05	2.81–9.05
60–99	1,245	11	7.13	3.37–15.10	22	15.46	8.12–29.46	26	11.77	6.66–20.79
p value (trend)			<0.001			<0.001			<0.001	
Geographic area										
Southwest	2,198	8	1		16	1		22	1	
South	1,195	8	1.70	0.64–4.56	11	1.24	0.57–2.68	11	1.08	0.51–2.27
Central	1,254	4	0.90	0.27–2.98	12	1.40	0.66–2.97	8	0.65	0.29–1.46
West	1,002	3	0.80	0.21–3.04	8	1.19	0.51–2.81	4	0.45	0.15–1.32
East	2,384	13	1.50	0.61–3.66	12	0.74	0.35–1.59	11	0.61	0.29–1.29
North	1,952	12	1.73	0.70–4.25	9	0.76	0.33–1.72	17	1.26	0.66–2.40
p value			0.60			0.58			0.20	
Smoking										
Never	5,124	11	1		29	1		45	1	
Ex	1,338	6	1.59	0.52–4.87	9	0.91	0.39–2.13	10	0.74	0.34–1.62
Light	2,133	13	3.69	1.48–9.19	20	2.33	1.20–4.55	7	0.55	0.24–1.30
Heavy	1,390	18	6.96	2.69–17.97	10	1.61	0.69–3.76	11	1.25	0.57–2.73
p value			<0.001			0.04			0.30	

[1]The model includes sex, age, geographic area and smoking status.

TABLE II – RELATIVE RISK (RR)[1] OF CANCER BETWEEN QUARTILES OF NITRITE, NITRATE AND NDMA INTAKE

Site of cancer	RR by quartile (95% CI)				*p* for trend
	1 lowest)	2	3	4 (highest)	
Head and neck					
Nitrite	1	0.46 (0.19–1.12)	0.76 (0.35–1.66)	0.83 (0.36–1.88)	0.77
Nitrate	1	0.72 (0.32–1.60)	0.50 (0.21–1.20)	0.84 (0.39–1.81)	0.95
NDMA	1	2.82 (1.11–7.17)	1.95 (0.73–5.17)	1.37 (0.50–3.74)	0.43
Stomach					
Nitrite	1	1.10 (0.58–2.11)	1.88 (1.01–3.49)	0.71 (0.28–1.78)	0.90
Nitrate	1	1.01 (0.56–1.84)	0.52 (0.25–1.08)	0.56 (0.27–1.18)	0.09
NDMA	1	1.03 (0.55–1.95)	0.78 (0.39–1.56)	0.75 (0.37–1.51)	0.39
Colorectum					
Nitrite	1	0.82 (0.45–1.48)	0.94 (0.50–1.78)	0.74 (0.34–1.63)	0.45
Nitrate	1	1.01 (0.52–1.92)	0.98 (0.51–1.87)	1.04 (0.54–2.02)	0.64
NDMA	1	1.47 (0.69–3.11)	1.95 (0.95–3.99)	2.12 (1.04–4.33)	0.47

[1]Adjusted for sex, age, municipality, smoking and energy intake.

TABLE III – RELATIVE RISK (RR)[1] OF CANCER BETWEEN QUARTILES OF FISH AND MEAT INTAKE

Quartile	Fish				Meat and meat products			
	Smoked and salted		Other		Cured		Other	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Head and neck								
1 (lowest)	1		1		1		1	
2	0.88	0.33–2.35	1.49	0.63–3.51	0.83	0.36–1.93	1.61	0.66–3.92
3	1.54	0.65–2.39	1.18	0.48–2.92	0.82	0.36–1.85	0.60	0.20–1.79
4 (highest)	1.01	0.43–2.39	0.77	0.31–1.93	0.89	0.43–1.84	1.54	0.57–4.12
Stomach								
1 (lowest)	1		1		1		1	
2	1.08	0.54–2.16	1.60	0.08–3.17	0.79	0.41–1.54	1.59	0.81–3.11
3	0.83	0.40–1.75	1.26	0.60–2.66	1.22	0.67–2.23	1.61	0.78–3.32
4 (highest)	0.98	0.49–1.96	0.93	0.43–2.00	0.49	0.22–1.06	0.88	0.35–2.22
Colorectum								
1 (lowest)	1		1		1		1	
2	1.45	0.64–3.30	1.07	0.53–2.17	1.48	0.77–2.84	0.93	0.48–1.84
3	1.81	0.81–4.03	1.60	0.81–3.16	1.28	0.63–2.57	1.71	0.90–3.28
4 (highest)	2.58	1.21–5.51	1.11	0.55–2.28	1.84	0.98–3.47	1.19	0.51–2.76

[1]Adjusted for sex, age, municipality, smoking and energy intake.

TABLE IV – RELATIVE RISK (RR)[1] OF CANCER BETWEEN BEER USERS AND NON-USERS IN A SUBPOPULATION

Site of cancer	Use of beer	Number of cases	RR	95% CI	*p* value for trend
Head and neck	No	17	1		
	Yes, below median	11	1.70	0.76–3.85	
	Yes, above median	11	1.92	0.84–4.37	0.79
Stomach	No	31	1		
	Yes, below median	8	0.70	0.31–1.59	
	Yes, above median	6	0.57	0.23–1.42	0.41
Colorectum	No	36	1		
	Yes, below median	7	0.74	0.32–1.74	
	Yes, above median	12	1.39	0.68–2.85	0.71

[1]Adjusted for sex, age, municipality and smoking.

other meat, and no associations were observed between the intake of any type of fish or meat and occurrence of cancers of the head and neck combined or of the stomach.

Beer consumption data were available in a sub-population; a non-significant association was present between beer consumption and cancers of the head and neck combined, but no association with respect to stomach or colorectal cancer was observed (Table IV). When the NDMA intake from beer was included in the total intake of NDMA from foods, the RRs were for head-and-neck cancer 1.95 (95% CI 0.62–6.15), stomach cancer 0.70 (95% CI 0.30–1.64) and colorectal cancer 2.23 (95% CI 1.02–4.86).

DISCUSSION

In the present cohort study, we found an increased risk of colorectal cancer among individuals with a high intake of NDMA. As far as we know, dietary nitrosamine intake has not previously been directly associated with colorectal cancer risk in humans. The association is plausible; nitrosamines from exogenous sources may reach colorectal tissues through both the gastro-intestinal tract and the blood. The human colonic lumen is also rich in amines and amides, which are substrates for nitrosation to *N* -nitroso compounds (Bingham *et al.*, 1996). Nitrosamines are potent carcinogens, and NDMA has been shown to induce formation of DNA adducts in human colonocytes (Autrup *et al.*, 1978), which may behave as an initiator of carcinogenesis (Tricker and Preussmann, 1991).

The main sources of NDMA in the present population were smoked/salted fish, cured meats/sausages and beer (Dich *et al.*, 1996). Accordingly, we also found an elevated risk of colorectal cancer among persons with a high intake of smoked and salted fish but no association for intake of fresh unsalted fish that would not appreciably contribute to nitrosamine intake. One previous case-control study suggested an increased risk of colon and rectal cancer associated with a more frequent consumption of dried or salted fish (Tajima and Tominaga, 1985). Previous cohort studies on total fish consumption have given inconsistent results (Bjelke, 1980; Willett *et al.*, 1990; Giovannucci *et al.*, 1994; Goldbohm *et al.*, 1994).

Cured meat products have been shown to contribute importantly to NDMA intake in several countries (Tricker and Preussmann, 1991; Dich *et al.*, 1996). In the present study, a non-significantly elevated risk of colorectal cancer was present among persons with a high intake of cured meat and sausages, but no association was observed for other meat products. Our finding is in agreement with those from cohort studies showing increased colorectal cancer risk associated with a high consumption of processed meats (Bjelke, 1980; Willett *et al.*, 1990; Giovannucci *et al.*, 1994; Goldbohm *et al.*, 1994).

Increased colorectal cancer risk has been associated with high beer consumption (Kune and Vitetta, 1992). A high concentration of NDMA has been found in beer, and beer has been estimated to be an important source of ingested nitrosamines in several Western countries (Scanlan, 1983; Hotchkiss, 1989). Beer consumption, investigated in part of the present population, was, however, not associated with colorectal cancer risk, which may be due to the fact that during recent decades the concentrations of NDMA in beer have greatly decreased, due to changes in the method of drying malt (Hotchkiss, 1989).

Although the association between nitrosamine intake and colorectal cancer observed here is plausible, it cannot be excluded that it may be due to confounding. In a study based on the same population, intake of NDMA was associated with potential risk factors of colorectal cancer (Dich *et al.*, 1996). Although the association between NDMA intake and colorectal cancer risk was

not explained by these or other factors adjusted for in the analyses, it remains possible that the association reflects some dietary or life-style habits related to development of the disease.

No significant associations were present between intake of NDMA or foods rich in NDMA and occurrence of other cancers of the gastro-intestinal tract. The only exception was a non-significantly elevated risk of cancers of the head and neck among individuals with a high intake of NDMA. This association is in line with the suggested importance of nitrosamine compounds in the development of upper aerodigestive tract cancers (Craddock, 1992; Mirvish, 1995). A population-based case-control study reported that NDMA intake was significantly associated with increased risk of upper aerodigestive tract cancers among individuals with low vitamin C intake (Rogers *et al.*, 1995). In the present study, no similar interactions were found between intake of NDMA and various anti-oxidant vitamins, possibly due to small numbers of cancer cases.

The lack of association between NDMA intake and stomach cancer occurrence is in agreement with the results of a previous prospective study on intake of nitrosamines and risk of gastric cancer (Chyou *et al.*, 1990) and with some (Risch *et al.*, 1985), but not all (Gonzáles, *et al.*, 1994; La Vecchia *et al.*, 1995; Pobel *et al.*, 1995), case-control studies. Although several case-control studies and a few cohort studies on foods containing *N* -nitroso compounds or their precursors, such as salt-preserved or smoked meat and fish, have shown increased gastric cancer risk, others have found no association (Kono and Hirohata, 1996).

Estimates of the strength of association between NDMA intake and cancer incidence in our and other epidemiological studies are apparently conservative. One reason may be the inability of dietary survey methods to estimate the intake of *N* -nitroso compounds. It is difficult to calculate the nitrosamine intake at an individual level for several reasons. The nitrosamine content of foods is greatly affected by environmental factors, and widely variable concentrations have been detected in the same types of food (Scanlan, 1983; Hotchkiss, 1989). During recent years, the levels of nitrosamines in foods such as cured meats and beer have been markedly reduced, due to changes in the methods of processing (Hotchkiss, 1989). In the present study, we estimated the intake of NDMA, the volatile nitrosamine most commonly detected in foods. NDMA, however, represents only a small fraction of the total amount of volatile and non-volatile nitrosamines provided by the diet and other environmental factors (Forman 1987; Bartsch and Spiegelhalder, 1996). The cohort study design used here results in an obvious advantage, especially in studies on diet and gastro-intestinal cancers since these diseases often cause intestinal discomfort and can provoke changes in food consumption. In studies with a long follow-up as here, however, the strength of association between dietary intake and risk of cancer may be under-estimated, due to changes in dietary habits during follow-up.

Dietary nitrites and nitrates have been suggested to be precursors of endogenous synthesis of nitrosamines and can therefore contribute to human cancer development (Forman, 1987; Mirvish, 1995). In the present cohort study, however, we found no significant association between intake of nitrates and nitrites and risk of gastro-intestinal cancers. Our results are in line with previous cohort studies (Chyou *et al.*, 1990; Van Loon *et al.*, 1997) and case-control studies (Eichholzer and Gutzwiller, 1998), which reported no increased risk of gastric cancer with high nitrate intake. As in studies from other countries, dietary nitrates of our Finnish study population were provided mainly by vegetables (Dich *et al.*, 1996). These foods are also good sources of vitamin C and other anti-oxidants which can efficiently block nitrosamine formation and possibly protect against cancer (Mirvish, 1995). Studies associating dietary nitrite intake and upper gastro-intestinal cancers have resulted in equivocal findings (Rogers *et al.*, 1995; Eichholzer and Gutzwiller, 1998).

In summary, we found an increased risk of colorectal cancer among individuals with a high intake of NDMA; this association could not be attributed to intake of other foods or nutrients. However, we found no notable association between intake of NDMA and incidence of stomach cancer or cancers of the head and neck combined. Although our result is in line with the hypothesized carcinogenic effect of nitrosamine compounds, its importance should be appraised against the fact that NDMA estimated in the present study represents only a small proportion of the various nitrosamine compounds detected in foods and derived from other environmental factors and endogenous synthesis. Better information on the nitrosamine composition of foods and dietary survey methods sufficiently sensitive to detect meaningful differences in their intakes are challenges to nutritional epidemiological research on the relationship between dietary nitrosamines and cancer occurrence.

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